Comparision of Conventional and Cutting Balloon Angioplasty for Congenital and Postoperative Pulmonary Vein Stenosis in Infants and Young Children

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Background: Pulmonary vein stenosis (PVS) is a rare and often lethal condition in children. The optimal treatment for congenital and postoperative PVS is unknown.

Methods and Results: We compared outcomes of conventional balloon angioplasty performed for PVS from 1999 to 2003 against cutting balloon angioplasty performed from 2004 to 2007. A total of 100 previously undilated pulmonary veins in 54 patients were studied: 48 veins dilated with conventional balloons and 52 with cutting balloons. Acute results included significantly reduced gradients and increased lumen diameters with both treatments. Acutely, cutting balloon angioplasty and conventional angioplasty yielded similar relative reduction of the PVS gradient (median 78% vs. 63%, P = 0.08) and increase in lumen diameter (median 77% vs. 59%, P = 0.07). There was one procedural death of a critically ill infant, and four cardiac arrests, but no adverse events necessitating surgical intervention. Survival free from reintervention was poor in both groups, and shorter in the cutting balloon group (73% at 1 month, 11% at 6 months, and 4% at 1 year) than in the conventional angioplasty group (77% at 1 month, 35% at 6 months, and 23% at 1 year; P = 0.01). Conclusions: Both conventional and cutting balloon angioplasty were effective at decreasing gradient and increasing lumen size acutely in patients with congenital and postoperative PVS, but reintervention was common with both treatments. Both methods of angioplasty provided limited benefit, and neither was curative for this complex disease. © 2010 Wiley-Liss, Inc.

Key words: congenital pulmonary vein stenosis; postoperative pulmonary vein stenosis; cutting balloon angioplasty

INTRODUCTION

Pulmonary vein stenosis (PVS) is a rare condition in children and that is frequently progressive and often lethal [1–3]. It can be congenital, in association with intracardiac abnormalities or in isolation, or acquired after surgical repair of congenital cardiovascular anomalies such as total or partial anomalous pulmonary venous return [1–4]. Historically, PVS has been treated with surgical and catheter-based therapies aimed at anatomic relief of obstruction within the lumen of individual vessels [3–13]. Transcatheter therapy typically consists of balloon angioplasty (including high-pressure and/or cutting balloon dilations) or stent placement. In addition to addressing proximal PVS, transcatheter techniques can be used to recanalize vessels with short

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segment atresia and sometimes to treat more distal disease of the lobar and/or segmental veins.

A small number of studies have shown that catheter-based interventions are safe but have limited success. Seale et al. showed short-term success with cutting balloon angioplasty in six patients with congenital PVS [12]. One larger study demonstrated acute effectiveness in increasing vessel diameter with standard and cutting balloon angioplasty, but these patients had PVS due to scarring after radiofrequency ablation, which is likely a different disease than congenital or postoperative pediatric PVS [13–16]. Small studies have also shown an acute increase in vessel diameter after stent placement, but with evidence of early restenosis [17–19]. Over the past two decades, multiple catheter-based techniques have been enlisted in efforts to treat congenital and postoperative PVS at Children’s Hospital Boston, with balloon angioplasty and cutting balloon angioplasty used most often. Understanding the outcomes and expected duration of benefit from standard and cutting balloon angioplasty may aid in determining which intervention provides the most improvement, but there have been no studies comparing these procedures.

METHODS

Patients

Patients <5 years of age who underwent angioplasty for congenital or postoperative PVS between 1999 and 2007 were ascertained from the computerized database of the Cardiovascular Program at Children’s Hospital Boston. Because many patients had multiple veins dilated, data were analyzed primarily by vein, except for demographic data, complications, and death, for which the patient was the index unit. All veins that had not been treated previously with transcatheter procedures were included: vessels dilated for the first time with conventional balloon angioplasty between the years of 1999–2003, and with cutting balloon angioplasty from 2004 to 2007 (the start of 2004 marks the routine use of cutting balloons at our center). Previously treated veins were not included. Additional interventions on the pulmonary vein at subsequent catheterization or surgery were analyzed separately and are discussed in the follow-up section. No patients had veins included in both groups.

Pulmonary Vein Dilation

The technique of entering the pulmonary veins has been described previously [20]. If no atrial septal defect existed, access to the left atrium was gained by transeptal puncture. A long-sheath was generally employed for angiography and delivery of balloons, and was always used for cutting balloon procedures. Various types of conventional balloons were used; cutting balloons ranged from 2.25 to 8 mm in diameter (Boston Scientific, Natick, MA). Balloon size was determined by the operator based on the angiographic appearance of the vessel. Use of a cutting balloon was determined by the operator, with no objective selection criteria. In some cases, cutting balloons were used for treatment of stenoses resistant to conventional balloon dilation, and in others a cutting balloon was used primarily. After cutting balloon angioplasty, the vein was frequently dilated with a conventional balloon no more than 1.5 mm larger than the cutting balloon, and occasionally this was followed with additional dilation with a larger diameter cutting balloon. Cutting balloons were inflated and deflated with a pressure monitoring gauge to a maximum pressure of 8–10 atm.

Hemodynamic Evaluation

Hemodynamic data were recorded from the catheterization reports. The PVS gradient was calculated as the difference between the mean pulmonary venous pressure and the mean LA pressure measured either simultaneously or on pull-back. If pulmonary venous pressure was not measured directly, or if the pulmonary vein was occluded by the catheter, the pulmonary arterial wedge pressure in the affected lobe was used.

Angiographic Analysis

All digital angiograms from the index catheterization were reviewed. Areas of obstruction were classified as focal, multifocal, or long-segment. Measurements of the minimum lumen diameter (MLD) were made in the anteroposterior and lateral projections before and after dilation. For multifocal or long-segment stenosis, the location of the balloon waist was used as the site for vessel measurement.

Data Analysis

The primary outcomes assessed were change in gradient and change in MLD. Data are expressed as mean ± standard deviation or mean and interquartile range. Preintervention and postintervention gradients were compared using paired t-test analysis. Similarly, the preintervention MLD and postintervention were compared using paired t-test. For comparison of conventional and cutting balloon angioplasty, the relative changes in gradient and MLD were compared using the Wilcoxon rank sum test. Time-dependent outcomes such as freedom from reintervention and survival were assessed with the Kaplan–Meier product-limit method. The primary aim of this study was not to assess survival, and analysis of factors associated with survival was not performed. To assess freedom from reintervention on the unit of interest in this study, namely,
RESULTS

Patients and Pulmonary Veins

A total of 100 consecutive previously undilated pulmonary veins in 54 patients were studied. Conventional balloon angioplasty was used in 48 veins in 30 patients between 1999 and 2003, and cutting balloons were used to treat 52 veins in 24 patients between 2004 and 2007. Demographic and diagnostic data are summarized in Table I. There were no differences in age or diagnoses of the patients between the two groups.

Catheterization and Balloon Dilation

Before intervention, the PVS gradient was higher in veins treated with a cutting balloon than conventionally treated veins. The MLD of affected pulmonary veins did differ between groups (Table II). Nineteen patients in the conventional angioplasty group and 15 in the cutting balloon group had suprasystemic right ventricular pressure. In 37 of the 52 vessels treated with a cutting balloon, a conventional balloon was used for postdilation after the cutting balloon angioplasty.

TABLE I. Demographic and Diagnostic Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Conventional balloon angioplasty</th>
<th>Cutting balloon angioplasty</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>30</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Median Age (months) [interquartile range]</td>
<td>9.0 [5.9–13.2]</td>
<td>6.8 [4.3–9.8]</td>
<td>0.23</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital PVS</td>
<td>6 (20%)</td>
<td>5 (21%)</td>
<td>0.89</td>
</tr>
<tr>
<td>Isolated</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Associated congenital heart disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative</td>
<td>24 (80%)</td>
<td>19 (79%)</td>
<td>0.89</td>
</tr>
<tr>
<td>Totally anomalous pulmonary venous return</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partially anomalous pulmonary venous return</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other defects</td>
<td>7</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Functionally univentricular heart disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral PVS</td>
<td>17 (57%)</td>
<td>17 (71%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Number of veins with PVS</td>
<td>3.1 ± 1.1</td>
<td>2.6 ± 1.3</td>
<td>0.45</td>
</tr>
<tr>
<td>Number of veins treated during study catheterization</td>
<td>1.5 ± 0.9</td>
<td>2.2 ± 1.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Veins</td>
<td>48</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>22 (46%)</td>
<td>19 (37%)</td>
<td>0.34</td>
</tr>
<tr>
<td>Left</td>
<td>23 (48%)</td>
<td>32 (61%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Confluence</td>
<td>3 (6%)</td>
<td>1 (2%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Previous pulmonary vein surgery</td>
<td>22 (46%)</td>
<td>24 (46%)</td>
<td>0.97</td>
</tr>
</tbody>
</table>

TABLE II. Baseline and Outcome Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Conventional balloon angioplasty</th>
<th>Cutting balloon angioplasty</th>
<th>P valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-intervention hemodynamic/anatomic data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary venous pressure (mm Hg)</td>
<td>21.8 ± 6.6</td>
<td>30.9 ± 11.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean PVS gradient (mm Hg)</td>
<td>11.8 ± 5.7</td>
<td>19.1 ± 11.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Minimum lumen diameter (mm)</td>
<td>2.3 ± 0.9</td>
<td>1.9 ± 0.9</td>
<td>0.02</td>
</tr>
<tr>
<td>Procedural data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum balloon size (mm)</td>
<td>5.2 ± 1.5</td>
<td>6.9 ± 1.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ratio of balloon diameter to minimum lumen diameter</td>
<td>3.2 ± 1.0</td>
<td>3.2 ± 1.6</td>
<td>0.78</td>
</tr>
<tr>
<td>Outcome data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median % change in gradient [interquartile range]</td>
<td>63 [43–78]</td>
<td>72 [60–83]</td>
<td>0.08</td>
</tr>
<tr>
<td>Median % change in MLD [interquartile range]</td>
<td>59 [38–84]</td>
<td>77 [47–141]</td>
<td>0.07</td>
</tr>
</tbody>
</table>

aP values for paired comparison of predilation and postdilation values.

Veins treated with either angioplasty modality, freedom from reintervention was assessed both as survival free from reintervention, and, to minimize the potentially confounding effect of a possibly survival bias in patients with fewer involved veins, freedom from intervention with patients censored event-free at the time of death if they died prior to any reintervention. Multivariable analysis was limited due to the fact that most of the potentially important covariates are patient-level rather than vein-level variables (see Limitations in Discussion). The study was approved by the Children’s Hospital Committee for Clinical Investigations. The authors had full access to the data and take full responsibility for its integrity.
Outcomes

Catheterization data. The directly measured PVS gradient decreased significantly in veins treated with both cutting and conventional balloon angioplasty, to postdilation gradients that did not differ between groups (Fig. 1a). There was no significant difference in relative gradient reduction between cutting balloon angioplasty and conventional angioplasty (Table II, \( P = 0.08 \)).

Angiographic data. The MLD increased significantly in both groups (Fig. 1b). There was no significant difference in the relative or absolute change in MLD after cutting and conventional balloon angioplasty (Table II, \( P = 0.07 \)), or in the absolute diameter change or postdilation MLD. The angiographic appearances before and after conventional and cutting balloon angioplasty are demonstrated in Figs. 2 and 3, respectively.

Adverse events. Four of the patients undergoing cutting balloon angioplasty had a cardiac arrest treated with cardiopulmonary resuscitation, and one had ventricular tachycardia treated with cardioversion. Among patients treated with conventional angioplasty, there was one vessel rupture resulting in hemopericardium that was managed with pericardial drain placement, and five patients experienced arrhythmias treated with...
intravenous medications. There was one procedural
death after cutting balloon dilation in a critically ill
patient with bilateral PVS who was receiving signifi-
cant hemodynamic support. There were no complica-
tions treated with surgical intervention.

Follow-up. During follow-up, a total of 31 patients
died, 19 of the 30 patients in the conventional angio-
plasty group and 12 of the 24 patients in the cutting
balloon group. By Kaplan–Meier analysis, overall sur-
vival was 91% at 1 month, 65% at 6 months, 49% at 1
year, and 31% at 5 years.

Repeat transcatheter intervention was performed in
25 of the 48 veins in the conventional angioplasty
group a median of 3 months after the initial procedure:
conventional angioplasty only in 18, cutting balloon
angioplasty in 2, and stenting in 5. Surgical reinterven-
tion was performed on 12 veins (25%) in the conven-
tional angioplasty group a median of 3 months after
angioplasty. Of the 52 veins in the cutting balloon
group, transcatheter reintervention was performed in 17
veins a median of 2.5 months after the initial proce-
dure: conventional angioplasty only in 2, cutting bal-
loon angioplasty in 13, and stenting in 2. Surgical rein-
tervention was performed in 11 vessels a median of 2
months postcatheterization. By Kaplan–Meier analysis,
overall survival free from reintervention was 75% at 1
month, 27% at 6 months, 15% at 1 year, and 5% at 2
years. As depicted in Fig. 4, survival free from rein-
tervention was shorter in the cutting balloon group (73% at 1 month, 11% at 6 months, and 4% at 1 year) than
in the conventional angioplasty (77% at 1 month, 35%
at 6 months, and 23% at 1 year; \( P = 0.01 \)). Because of
the potentially confounding effects of survival disad-
vantage in patients with multiple involved veins, free-
dom from reintervention was also analyzed with
patients censored event-free at the time of death if they
died prior to any reintervention. On this analysis, free-
dom from reintervention was also shorter in veins ini-
tially treated with cutting balloon angioplasty (80% at
1 month, 17% at 6 months, 4% at 1 year) compared to
veins treated with conventional angioplasty (81% at 1
month, 43% at 6 months, 34% at 1 year).

Fig. 3. Angiograms in stenotic common left pulmonary vein (a) before and (b) after cutting
balloon angioplasty. The white arrow indicates the focal stenosis prior to dilation.

Fig. 4. Kaplan–Meier curve depicting freedom from reinter-
vention on individual pulmonary veins after angioplasty with
conventional or cutting balloons.
DISCUSSION
Transcatheter Therapy for PVS
In our experience, both conventional and cutting balloon angioplasty acutely increased MLD and decreased PVS gradients in infants and young children with congenital and postoperative PVS, although reintervention was common in both groups and occurred soon after the initial intervention. PVS is a progressive disease and, although conventional and cutting balloon angioplasty may provide temporizing therapy in patients who develop respiratory symptoms from reobstruction, no known intervention has been shown to stop the disease. In the only other study to report cutting balloon angioplasty in pediatric PVS, three patients died, two had continued pulmonary hypertension, and the last remained critically ill [12]. Only one small study looked at stent placement in the catheterization laboratory in four patients with PVS, and six of seven vessels restenosed within only a few months [19]. The adult literature on angioplasty and stenting after radiofrequency ablation-induced PVS also supports the regularity of restenosis, although this patient population represents a very different disease process.

PVS persists and continues to progress despite interventions in the operating room or the catheterization laboratory. With focal therapy providing only transitory relief, the possibility of systemic or nonlocalized treatment remains a possibility. This cohort of patients undergoing cutting and conventional balloon angioplasty might serve as a comparison group for patients undergoing other modes of treatment.

Technical Considerations
There are several important technical considerations around cutting balloon angioplasty of pulmonary veins. Use of a long sheath is important for stable advancement of the cutting balloon into the pulmonary vein, as the balloon may not track well. The long sheath also allows for predilation and postdilation angiography, and is essential for resheathing and removal of the cutting balloon. Because the catheter course may form a relatively tight curve, particularly when dilating lower lobe veins, reSheathing the cutting balloon typically requires careful maneuvering of the sheath, and may be facilitated by oversizing the long sheath. Proper dilation should be performed with a gauge for steady inflation and deflation to optimize refolding. Because of the thickness of the intima and media of the stenotic vein, it may be beneficial to perform staged cutting balloon angioplasty, with intermediate postdilation using conventional or high-pressure balloons. Also, as with conventional angioplasty, distal dilations often facilitate stability of the balloon for proximal dilation.

Limitations
Patients were not assigned randomly to conventional or cutting balloon angioplasty. Similarly, patients in the conventional angioplasty group were treated before cutting balloons were used routinely at our center, whereas cutting balloons have been used in most patients treated since 2004. Criteria for use of cutting balloons was not standardized, and may have been limited to treatment of resistant lesions in some patients and used primarily in others. Also, the retrospective nature of the study required review of catheterization documentation to obtain hemodynamic measurements. In cases of severe PVS, it may be difficult to obtain an accurate pressure in the pulmonary vein because the catheter may be obstructing the stenotic lumen or against the wall of the vein, effectively yielding a pulmonary vein wedge pressure. Pulmonary artery wedge pressures were used as surrogates in such cases, but may not be as accurate as a directly measured pressure in the vein. Thus, there may be inaccuracies in our hemodynamic measurements. Measurements of MLD were dependent on, and potentially limited by, the quality of angiography. Although our institutional practice is relatively consistent, angiography in these cases was not conducted according to a standardized protocol, and measurements may be of variable accuracy. Multiple interventional cardiologists performed the procedures analyzed for this study, and differences in technique and practice may have biased our findings. The degree of PVS may not be fully represented simply by MLD and gradient, with different patients exhibiting clinical symptoms at different values. A patient may present to the catheterization laboratory because of a clinical change or because of an imaging change unrelated to clinical status. Thus, the time to send a patient to intervention is influenced greatly by practitioner judgment. Also, as we have developed more experience with intervening on obstructed pulmonary veins, our treatment of these patients, including thresholds for and aggressiveness of intervention, may have also evolved. These disparities, as well as differences in our referral population, may have biased our cohorts and our results. Analytically, it was not possible to adequately adjust the analyses of survival free from reintervention or freedom from reintervention because most of the other potentially important covariates, such as unilateral/bilateral disease, congenital/postoperative PVS, and age at initial intervention, are patient-level variables, which is a potential source of bias for a number of reasons, including the fact that prognosis may be worse in patients with a larger number of involved veins. This study did not include a formal cost analysis, and it may be important to consider this factor in choosing balloons.
for PVS dilation, as cutting balloons are generally two to four times more expensive than the conventional angioplasty balloons that we use for this disease.

CONCLUSIONS

Both conventional and cutting balloon angioplasty were acutely effective at increasing MLD and decreasing obstruction in infants and young children with congenital and postoperative PVS. Cutting balloon angioplasty did not appear to offer any acute benefits over conventional angioplasty, and may be most effective at relieving PVS that is resistant to conventional angioplasty, although this study did not test that hypothesis. Despite acute angiographic and hemodynamic improvements after angioplasty, reintervention was performed frequently and soon after the initial intervention in both groups. From these findings, we conclude that angioplasty with conventional or cutting balloons alone does not offer long-term improvement for infants and young children with congenital and postoperative PVS. The utility and longer-term effectiveness of angioplasty in a more comprehensive management strategy cannot be determined from this study.

REFERENCES
